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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/555,674 08/03/00 GABIZON

A 9325-0007.10

001444 HM12/1004
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EXAMINER

GLITTMAN, H

ART UNIT

PAPER NUMBER

1651

DATE MAILED:

17
10/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/555,674

Applicant(s)

GABIZON ET AL.

Examiner

Harry J Guttman

Art Unit

1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 31-53 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 31-53 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: See Continuation Sheet.

Continuation of Attachment(s) 6). Other: Kedar et al. (1993) and Ten Hagen et al. (1997).

DETAILED ACTION

Continued Prosecution Application

The request filed on August 6, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/555,674 is acceptable and a CPA has been established. An action on the CPA follows.

Status of the Claims

Claims 31-53 are pending.

Claims 31-53 are examined on their merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 recites "liposomal doxorubicin". This phrase lacks antecedent basis because the parent claim (claim 31) recites "a non-encapsulated chemotherapeutic drug". This claim is not considered further on its merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-33, 38-40, 42-44, 50, 51 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Fondy et al. (WO 9013293).

Fondy et al. teach the use of liposomal encapsulation of IL-2 (page 21 lines 19-26 and page 18 lines 15-21). Multilamellar vesicles (MLV) are taught as delivery vehicles (page 16 lines 10-24 and page 17 lines 4-8). Fondy et al. teach administration of IL-2 after that of cytochalasin, which may be in liposomes or not (page 21 lines 19-26 and pages 13-15). Fondy et al. teach the use of non-encapsulated doxorubicin in combination with liposome-encapsulated IL-2 (page 21 lines 18-40).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fondy et al. (WO 9013293) in view of Anderson (US 54009698) and Ochoa et al. (US 5316763).

The disclosure and teachings of Fondy et al. (WO 9013293) are given above. Fondy et al. do not disclose or teach the specific lipids or lipid ratios of the MLV for IL-2 incorporation as claimed by Applicant.

Anderson (US 54009698) disclose the use for anti-tumor therapy of MLV encapsulated IL-2 (example 4). The MLVs included DMPC and DMPG in a ratio of 7:3 (example 1). They discuss the stability benefits of MLVs compared with unilamellar vesicles (e.g., column 6 6-27).

Ochoa et al. (US 5316763) disclose the use for anti-tumor therapy of MLV encapsulated IL-2 (column 7 lines 13-42, and example 2). The MLVs of example 2 used 100% DMPC (i.e., no DMPG added).

At the time the invention was made, one of ordinary skill in the art would have been motivated to use the formulation of IL-2 encapsulated with MLV having a DMPC:DMPG ratio of 9:1, because (1) the use of MLV-encapsulated IL-2 having DMPC:DMPG ratio of 7:3 and 1:0 (i.e., no DMPG) were known in the art for benefits of added stability and added anti-tumor effects of IL-2, and (2) the claimed ratio would be readily expected to perform similarly since the ratios from two of the above-cited references bracket that of the claimed ratio. Finally, the choice of the exact ratio of

DMPC:DMPG is a matter of routine optimization which is well within the purview of one of ordinary skill in the art.

Claims 42-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fondy et al. (WO 9013293) in view of Kedar et al. (Biological Response Modifiers, 1993), Ten Hagen et al. (March 1997), Anderson (US 54009698) and Ochoa et al. (US 5316763).

The disclosure and teachings of Fondy et al. (WO 9013293) are given above. Fondy et al. do not disclose or teach (1) the specific lipids or lipid ratios of the MLV for IL-2 incorporation as claimed by Applicant, and (2) the use of doxorubicin separately encapsulated by polyethylene coated liposomes in combination with liposome-encapsulated IL-2.

Kedar et al. (Biological Response Modifiers, 1993) disclose the use of IL-2 and doxorubicin for anti-tumor therapy. Both IL-2 and doxorubicin were used in their free form (i.e., without encapsulation) and they also were encapsulated separately in liposomes that had a 5 mole% of lipid derivitized with PEG 1900.

Ten Hagen et al. (March 1997) disclose the use for antitumor therapy of STEALTH liposome-encapsulated TNF- α (a known cytokine) in combination with STEALTH liposome encapsulated doxorubicin compared to separate administration. The STEALTH liposome has lipids that have PEGs attached to the polar group.

Anderson (US 54009698) disclose the use for anti-tumor therapy of MLV encapsulated IL-2 (example 4). The MLVs included DMPC and DMPG in a ratio of 7:3

(example 1). They discuss the stability benefits of MLVs compared with unilamellar vesicles (e.g., column 6 6-27).

Ochoa et al. (US 5316763) disclose the use for anti-tumor therapy of MLV encapsulated IL-2 (column 7 lines 13-42, and example 2). The MLVs of example 2 used 100% DMPC (i.e., no DMPG added).

At the time the invention was made, one of ordinary skill in the art would have been motivated to use the formulation of IL-2 encapsulated with MLV having a DMPC:DMPG ratio such as 9:1, because (1) the use of MLV-encapsulated IL-2 having DMPC:DMPG ratio of 7:3 and 1:0 (i.e., no DMPG) were known in the art for benefits of added stability and added anti-tumor effects of IL-2, and (2) the claimed ratio would be readily expected to perform similarly since the ratios from two of the above-cited references bracket that of the claimed ratio. Finally, the choice of the exact ratio of DMPC:DMPG is a matter of routine optimization which is well within the purview of one of ordinary skill in the art.

At the time the invention was made, one of ordinary skill in the art would have been motivated to use liposomal encapsulated doxorubicin because (1) the beneficial effects of encapsulating doxorubicin in PEG-liposomes (i.e., compared to free doxorubicin) for anti-tumor therapy were well known in the art, and (2) they have been used in conjunction with encapsulated IL-2 as an anti-tumor therapy. Further, the synergy between liposome-encapsulated cytokines and liposome-encapsulated doxorubicin to enhance anti-tumor activity was known in the art, as demonstrated by Ten Hagen et al. (1997, last sentence).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

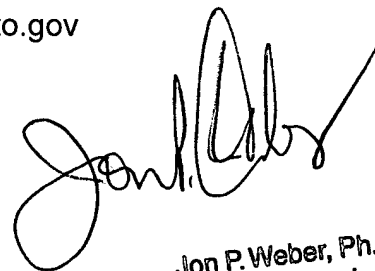
Any inquiry concerning this communication should be directed to Harry J. Guttman, Ph.D. at telephone number (703) 305-0159. The examiner can normally be reached during the hours of 07:30 to 16:00 Eastern Time, Mon.-Thurs. If attempts to reach the examiner by telephone are unsuccessful, a message may be left on the voice mail. The fax number for Art Unit 1651 is (703) 308-4242 or 305-3014. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. My supervisor, Michael Wityshyn, may be contacted at (703) 308-4743.

All internet e-mail communications will be made of record in the application file. PTO employees will not communicate with applicant via internet e-mail where sensitive data will be exchanged or where there exists a possibility that sensitive data could be identified or exchanged unless there is of record an express waiver of the confidentiality requirements of 35 U.S.C. 122 by the applicant. See the Interim Internet Usage Policy published in the Patent and Trademark Office Official Gazette on 25 February 1997 at 1195 OG 89.

H.J.G. 2 October 2001



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